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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/466,698	06/06/95	SANSONETTI P	2356.0043-02

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EXAMINER	
CAPUTA, A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 08/466,698	Applicant(s) Sansonetti et al.
	Examiner Anthony C. Caputa	Group Art Unit 1645

☒ Responsive to communication(s) filed on *17 Apr 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-8, 10, and 13-24* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 10, and 13-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

2. Applicants amendment and response was received 4/17/98 and entered as Paper No. 25. Claims 1-8, 10, 13, 14, and 15-24 are pending.

Claim Rejections - 35 USC § 112/1st paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 10, 13, 14 and newly submitted claims 15-24 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the Office Action mailed 4/30/97 (see Paper No. 13).

As set previously, it is apparent that numerous modified Shigella are required to practice the claimed invention.

In the instant case the construction of claimed Shigella mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. Due to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation. In view of the foregoing the

only means by which applicants can provide an enabling disclosure for the Shigella mutants is by depositing said mutants and limiting the claims to the deposited mutants.

Applicants urge that the specification provides sufficient teachings for one skilled in the art to practice the claimed invention (see page 5 of applicants' response submitted after final dated October 9, 1997-Paper No. 20). Applicants state that the specification teach of methods of modification to employ in order to inactivate the genes. These arguments are not considered persuasive. The decisional law has held the mere recitation in the specification of a broad concept does not necessarily provide a sufficient basis for broadly claiming it (i.e. transposon mutagenesis). See Ex parte Gardner 157 USPQ 162 (Bd. Pat. Appls and Interf. 1967), In re Cavallilo, 127 USPQ 202 (CCPA 1969). The fact that the terms in a claim are the same as those in the specification does not prevent the claims from being rejected as unduly broad if they define subject matter not define subject matter not described to be the actual invention by means of adequate representative samples. See in re Lund, 153 USPQ 625 (CCPA 1967). In the instant case the construction of claimed Shigella mutants requires knowledge of the nucleotide sequence of genes (i.e. for production and use of iscA, virG, aerobactin, enterochelin), which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. Due to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation.

While it would appear techniques are known in the art for inactivation, as pointed out by applicants it is **not** routine in the art to screen for positions within the DNA sequence of the gene so that it does not invade the cells, spread within infected cells, or not produce toxins. Because the specification does **not** disclose :

- which regions of the genes are responsible for biological activity;
- the number of nucleotides which must be deleted or inserted;

- the identity of the genes that are responsible for invading cells, not producing toxins, etc.;

-identity of genes that code for use of aerobactin or enterochelin,

-more than one genes would be expected to be involved in toxin production, spreading, and/or invasion;

- no guidance as to which of the essentially infinite possible choices is likely to be successful;

modifications that can be made to inactivate the genes is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

Applicants argue Nassif et al. (see Exhibit 1), Baudry et al. (see Exhibit 2), and Maurelli et al (see Exhibit 3) contain the teachings necessary for screening the *Shigella* genes involved in the invasion of cells, spreading within infected cells, etc.. Applicants arguments were not found to be persuasive. Baudry et al. submitted by applicants (see response submitted after final dated October 9, 1997-Paper No. 20-Exhibit 2) sets forth "The available data indicate that the invasive ability of *S. flexerni* is a very complex phenomenon which involves many genes and a large array of polypeptides" and "Whether all these gene products are directly involved in the interaction with the cells, or whether a pool of polypeptides is necessary for transformation and/or correct positioning of a unique product is yet not known" (see page 3411, last para) . In view of: 1) the statements of Baudey et al pointed out above; 2) the assay procedures of Nassif et al. are only directed to one gene which encodes for aerobactin; 3) case law sets forth the general process of isolating DNA does not mean that the claimed specific compound was precisely envisioned or obvious (see *In re Deuel* 34 USPQ2d 1210 Fed Cir 1995) and; 4) modifications that can be made to inactivate the genes are unpredictable as set forth above the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement is maintained.

Applicants argue that the Examiner did not address the teachings of Maurelli et al. Applicants arguments are not persuasive. Given the statements by Baudry et al. And disclosure of Nassif a skilled artisan would not be enable to practice the claimed invention, given the teachings of Maurelli et al.. Further, as set forth previously, applicants arguments are not sufficient to obviate the rejection in view of *Fliers v. Sugano,* 25 USPQ 2d 1601 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., and Genetics Institute., Inc.,* 18 USPQ 2d 1016 (Fed. Cir. 1991) as set forth in the prior Advisory Action mailed 9/26/97. Moreover the teachings of Maurelli are not sufficient to obviate the rejection since the teachings of Maurelli et al are not commensurate with the claimed invention since Maurelli only provides guidance of the virR gene.

Applicants argue Prentki and Krisch contain the teachings necessary for screening the *Shigella* genes involved in the invasion of cells, spreading within infected cells, etc.. Applicants arguments were not found to be persuasive. Prentki et al. submitted by applicants sets forth "Several difficulties, however, are associated with he use of transposons mutagens. First, some transposable elements exhibit a bias for the position of integration into the target molecule, either in a sequence specific manner ..., or through a strong preference for A/T rich regions.... Second, transcriptional activity into adjacent DNA has been reported.., sometimes complicating the phenotypic and genetic characterization of insertion mutants. Finally, once inserted into the target molecule, transposable elements have the capacity to generate DNA rearrangements such as deletions or inversions.". (See page 311; Column 2). In view of the statements of Prentki et al. it would appear the method disclosed by Prentki et al. does not enable the claimed invention contrary to applicants arguments (see pages 7-10 of Paper No. 25).

Applicants submits additional references are indicative of the skill in the art at the time of the application was filed (see Exhibits 2-9). Applicants arguments are not persuasive. Exhibits 2-9 are not indicative to enable one skilled in the art to practice the claimed invention since said Exhibits are not commensurate in scope with the claimed invention. The claims are not limited to

a *Shigella* invasion plasmid. Moreover, Exhibits 2-9 are not sufficient to obviate the rejection as evidence by the statements as set forth by Sasakawa et al. (1986 and 1988) and Baudry et al.

In 1986 and June of 1988 it would appear a skilled artisan was trying to determine the detailed regions associated with virulence as exemplified by Sasakawa et al who sets forth "We are currently trying to determine the detailed regions associated with virulence conferred by the large plasmid" (see page 33, last para. Of Sasakawa et al. 1986-Exhibit 3) and Sasakawa et al., 1988 who sets forth "We are currently undertaking studies to characterize the cistrons of the virulence associated regions and their protein products in order to define their role in the pathogenesis of bacillary dysentery (see page 2483, last para of Sasakawa et al. 1988-Exhibit 4). Additionally, Baudry et al. submitted by applicants (see response submitted after final dated October 9, 1997-Paper No. 20-Exhibit 2) sets forth "The available data indicate that the invasive ability of *S flexerni* is a very complex phenomenon which involves many genes and a large array of polypeptides" and "Whether all these gene products are directly involved in the interaction with the cells, or whether a pool of polypeptides is necessary for transformation and/or correct positioning of a unique product is yet not known" (see page 3411, last para) .

Applicants submit additional references (Exhibits 10-15) to indicate one skill in the art at the time of the application was filed had knowledge of aerobactin and enterocholin synthesis. Applicants arguments are not persuasive to obviate the rejection. Exhibits 10, 11, and 13-15 are not indicative to enable one skilled in the art to practice the claimed invention since said Exhibits are not commensurate in scope with the claimed invention. Exhibits 10, 11, and 13-15 are directed to *E coli* and not *Shigella* as claimed. Finally Exhibit 14 is not sufficient to obviate the rejection since the claims are not limited to the aerobactin genes as described by Lawlor et al (Exhibit 14). For the reasons set forth above in the prior Office Action said rejection is maintained.

5. Claims 1-8, 10, 13, 14 and newly submitted claims 15-24 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. The prior provisional rejection of Claim 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100 is withdrawn in view of applicants' amendment.

7. The prior objection of claims 1-8, and 10 is withdrawn in view of applicants arguments.

8. The prior rejection of claims 2-8, and 10 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment and arguments.

9. The prior objection to the specification is withdrawn in view of applicants' amendment

10. Newly amended claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed provides no support for claiming a Shigella mutant wherein the Shigella is other than SC501, SC504, SC 505, and SC 506. Th courts set forth any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984).

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196.

Papers related to this application may be submitted to Art Unit 1645 by facsimile transmission. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The Fax number is (703)-308-4242

Anthony C. Caputa, Ph.D.
July 20, 1998

ANTHONY C. CAPUTA
PRIMARY EXAMINER